Alkene Hydrocyanation

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Mild Cobalt-Catalyzed Hydrocyanation of Olefins with Tosyl Cyanide**

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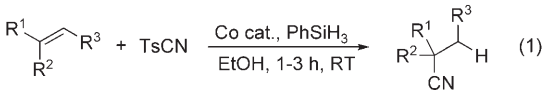
Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

The diverse transformations in which nitriles participate[1] (for example, $RCN \rightarrow RCO_2H$, $RCONH_2$, RCHO, RCH_2NH_2, and RCN_4, as well as Pinner and Ritter reactions) place them among the most versatile intermediates in organic chemistry. Although the displacement reactions of leaving groups by cyanide constitute the most common access routes to these, direct olefin hydrocyanation is an attractive alternative. In our continuing interest in the development of functionalization reactions of olefins, we have discovered a hydrocyanation reaction that is conceptually different from the existing methods that are available. Herein, we report the cobalt-catalyzed hydrocyanation of non-activated olefins using *p*-toluenesulfonyl cyanide (TsCN) and phenylsilane in ethanol at room temperature [Eq. (1)].

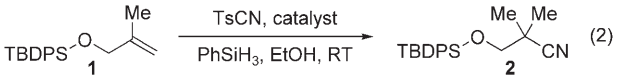


(1)

The conversion of an olefin into a nitrile by hydrocyanation has long been recognized to be important, because of the useful, simple building blocks that would be accessible. Additionally, a mild and versatile procedure for such a process would facilitate novel strategic approaches for the synthesis of complex molecules. The most notable advance in olefin hydrocyanation stems from the discovery that certain nickel complexes catalyze the addition of hydrogen cyanide to alkenes,[2] a reaction that has been studied in mechanistic detail.[3] For the reported system, aryl alkenes[4] and dienes[5] have been shown to react well at elevated temperatures, whereas non-activated olefins[6] require the addition of Lewis acid activators such as $AlCl_3$. The enantioselective version has also been documented, primarily for aryl-substituted alkenes.[4b,7] A typical reaction is commonly run at 60–120 °C, and the alkene substrate is often used in excess (up to 2 equiv). Recently, a low-temperature protocol for the asymmetric hydrocyanation has been documented albeit for 1,3-dienes only.[8]

We have recently documented that simple cobalt complexes effect the hydrohydrazination ($RO_2CN{=}NCO_2R$ + alkene $\rightarrow$ *N*-alkyl hydrazine)[9] and hydroazidation (TsN_3 + alkene $\rightarrow$ alkyl azide)[10] reactions of olefins. The methods display broad substrate scope for a wide range of alkenes.[11] We have been keen in investigating whether similar protocols could be developed for C–C bond-forming processes, which would considerably expand the reaction and product space accessible from olefins. We decided to test our hypothesis in the context of the olefin hydrocyanation reaction, because such a process would not only perhaps exhibit complementary substrate scope to that observed with Ni catalysts, but it would also open up new possibilities for the synthesis of useful building blocks.

At the outset of our investigations *tert*-butyl-(2-methylallyloxy)diphenyl silane (**1**) was employed as a test substrate in combination with TsCN[12] as reagent [Eq. (2)]. We



(2)

proceeded to screen and examine complexes of cobalt that had proven successful in previous investigations involving olefin heterofunctionalization (Figure 1).

The reaction of 1.5 equiv of TsCN together with 1 equiv of phenylsilane in the presence of Co complex **3** afforded nitrile **2** in 29% yield [Eq. (2)]. Complex **4**, prepared in situ, with 1 equiv of tetramethyldisiloxane (TMDSO) provided the hydrocyanation product **2**, albeit in a meager 19% yield; and the same reaction with $[Mn(dpm)_3]$[13] resulted in no conversion at all. We then turned our attention to the investigation of Co complexes incorporating salen ligands.[14] We were pleased to see that Co^{III} catalyst (±)-**5a** displayed good activity, leading to isolation of nitrile **2** in 81% yield after 3 h. As *t*BuOOH is known to facilitate the initiation period in reactions we have studied with these catalysts,[10,15] its effect on the reaction at hand was tested next. Indeed, addition of 30 mol% of *t*BuOOH shortened the reaction time to 2 h and increased the yield to 88%. In subsequent studies, we observed that the sterically less hindered catalysts **5b** and **6b**[16] were less active; consequently, we prepared and

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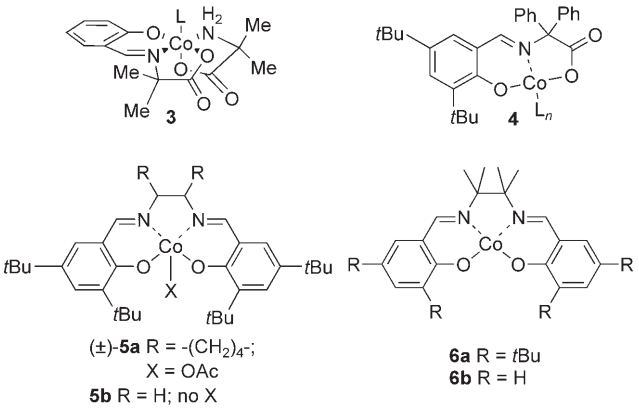


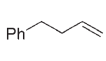
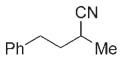
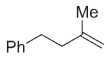
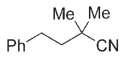
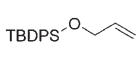
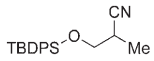
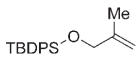
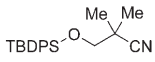
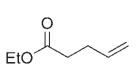
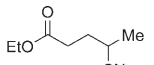
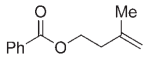
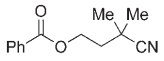
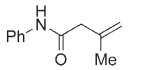
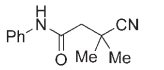
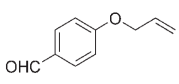
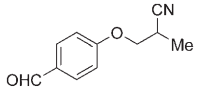
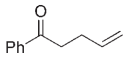
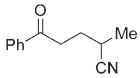
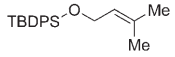
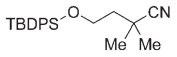
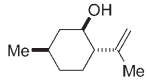
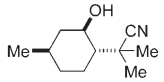
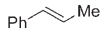
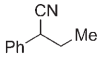
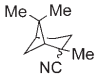
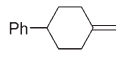
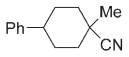
Figure 1. Catalysts screened in the hydrocyanation reaction.

examined the tetramethyl-substituted salen ligand[17] and its corresponding cobalt complex **6a**. When 1 mol% of **6a** was mixed with alkene **1**, 1.5 equiv of TsCN, and 1 equiv of $PhSiH_3$ in EtOH at room temperature, nitrile **2** was isolated in 99% yield within 1 h. Importantly, the addition of *t*BuOOH was not necessary, and furthermore, we were able to decrease the amount of TsCN to 1.2 equiv without influencing the yield.

The effect of other silanes on the reaction was tested next. Et_3SiH was not active at all, and 3 equiv of Ph_2MeSiH gave only 51% of the nitrile **2** after 19 h. Me_2PhSiH (3 equiv) and TMDSO (2 equiv) provided the desired product **2** in yields of 83% and 87%, respectively. These two silanes, however, required longer reaction times (4–6 h).

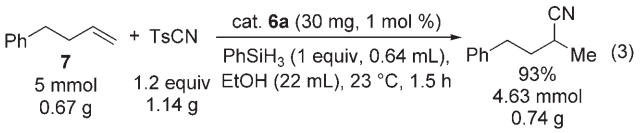
The scope of the hydrocyanation reaction employing both protocols with catalysts **5a** and **6a** (Table 1) was next examined. In general, catalyst **6a** is more active, giving equal or higher yields and shorter reaction times than **5a**. All of the monosubstituted, 1,1-disubstituted, and trisubstituted olefins showed excellent Markovnikov selectivity as linear nitriles were never observed. In the case of 1,2-disubstituted alkenes conjugated to an aromatic ring (entries 12 and 13, Table 1), cyanation occurred only at the benzylic position. Simple alkenes, protected alcohols, esters and amides (entries 1–7, Table 1) are well tolerated for the reaction, with both catalysts performing equally well. In the presence of an aldehyde or keto functionality the difference between the two catalytic systems becomes apparent (entries 8 and 9, Table 1), with **6a** being more effective and providing the corresponding products in higher yields. A similar trend was observed with a trisubstituted olefin (entry 10, Table 1). Styrene derivatives (entries 12 and 13, Table 1) provided benzylic nitriles in moderate yields. Interestingly these substrates proved excellent in the hydrohydrazination[9] but failed in the hydroazidation[10,11b] reaction. α,β-Unsaturated esters and unactivated 1,2-disubstituted cyclic olefins such as cyclohexene failed to provide the product of hydrocyanation, thus representing the limitations of this process. Compounds with an exocyclic double bond (entries 14 and 15, Table 1), however, are good substrates for the reaction. It is worth noting that the recent advances in enantioselective biotransformations of nitriles, involving hydratases, nitrilases, and amidases, provide powerful approaches for the preparation of optically active acids in industrial processes. Thus we envision that a particular advantage of the method we describe to provide access to nitriles will result when its use is coupled to enzymatic resolution. This effectively amalgamates a convenient chemical transformation that is outside the realm of enzyme-mediated reactions (olefin hydrocyanation) with what is, by contrast, a process that is mainstream for enzymes ($RCN \rightarrow RCO_2H$).[1d,18]

Table 1: Hydrocyanation reaction of olefins.

Entry	Alkene	Product	Yield [%] **5a**[a]	Yield [%] **6a**[b]
1			99	99
2			95	99
3			84	95
4			88	99
5			82	89
6			99	96
7			86	87
8			64	81
9			40	91
10			48	92
11			73	71
12			45	55
13			63	64
14			88[c]	60[c]
15			74[d]	81[e]

[a] Conditions: catalyst **5a** (1 mol%), alkene (0.5 mmol), TsCN (0.75 mmol), *t*BuOOH (30 mol%), $PhSiH_3$ (0.5 mmol), EtOH (3 mL), argon, 23 °C. [b] Conditions: catalyst **6a** (1 mol%), alkene (0.5 mmol), TsCN (0.6 mmol), $PhSiH_3$ (0.5 mmol), EtOH (2.5 mL), argon, 23 °C. [c] d.r. could not be determined. [d] d.r. = 17:1. [e] d.r. = 3:1

To establish the practicality of the process we scaled up the reaction tenfold. Using only 1 mol% of catalyst **6a** and 4-phenylbutene (**7**) as substrate, the hydrocyanation product was obtained in 93% yield [Eq. (3)]. Thus, the protocol represents a convenient means to rapidly access nitriles from olefins without recourse to specialized techniques that would



require handling HCN or elevated pressures and temperatures.[19] Moreover, once the reaction has reached completion, simple removal of solvent followed by chromatography on silica gel furnishes the desired nitrile product.

In summary, we have documented a conceptually new hydrocyanation reaction of non-activated olefins that gives access to secondary and tertiary nitriles. It is a transformation for which to date few procedures have been available. The salient features of this process are the broad functional-group tolerance, mild reaction conditions (room temperature, EtOH as solvent), readily available starting materials (TsCN, $PhSiH_3$, catalysts, olefins), and ease of execution. Moreover, the reaction can be conducted at preparatively useful scales and essentially no workup is necessary. Further exploration of the reaction to get deeper insight into this process is underway, and the results will be reported as they become available.

Experimental Section

General procedure A: Catalyst **5a** (3.3 mg, 0.005 mmol, 1 mol%) was dissolved in EtOH (2 mL; absolute, Merck) at room temperature under argon. After 2 min alkene (0.5 mmol) was added followed by TsCN (144 mg, 0.75 mmol, 1.5 equiv; 95% purity, Aldrich,). *t*BuOOH (5.5 M solution in decane, 25 μL, 0.14 mmol, 0.30 equiv) was added followed by $PhSiH_3$ (98% ACROS, 62 μL, 0.5 mmol, 1.0 equiv) and another portion of EtOH (1 mL). The resulting solution was stirred at room temperature, and the reaction was monitored by TLC. After completion (1–3 h) the solvent was removed by evaporation, and the crude mixture purified by flash chromatography to afford the corresponding nitrile.

General procedure B: Catalyst **6a** (3 mg, 0.005 mmol, 1 mol%) was dissolved in EtOH (2 mL; absolute, Merck) at room temperature under argon. After 2 min alkene (0.5 mmol) was added to the red solution followed by TsCN (115 mg, 0.6 mmol, 1.2 equiv; 95% purity, Aldrich). Finally $PhSiH_3$ (62 μL, 0.5 mmol, 1.0 equiv, 98% purity, ACROS) was added, and another portion of EtOH (0.5 mL). The resulting solution was stirred at room temperature, and the reaction was monitored by TLC. After completion (1–3 h) the solvent was removed by evaporation and the crude mixture purified by flash chromatography to afford the corresponding nitrile.

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